

Appl. No. 09/975,317
Amendment dated: August 27, 2003
Reply to OA of: May 1, 2003

This listing of claims will replace all prior versions and listings of claims in the application.

Listing of Claims:

Claims 1-50(canceled).

51(new). A method of detecting myocardial ischemia in a human or non-human body, said method comprising administering to said body a contrast medium consisting essentially of a physiologically acceptable manganese complex or salt thereof at a dosage of 0.001 to 0.2 mmol/kg bodyweight, subjecting said body to a magnetic resonance imaging procedure capable of generating images with time intervals of less than 0.5 seconds and thereafter providing a series of images of the myocardium of said body and identifying regions of abnormal blood flow.

52(new). A method as claimed in claim 51 wherein said magnetic resonance imaging procedure is one capable of generating images with time intervals of less than 100 milliseconds.

53(new). A method as claimed in claim 51 wherein said imaging procedure is a gradient echo or echo planar imaging procedure.

54(new). A method as claimed in claim 53 wherein said imaging procedure is an inversion recovery echo planar imaging procedure.

55(new). A method as claimed in claim 53 wherein said imaging procedure is one in which TI (inversion time) is 100 to 800 msec.

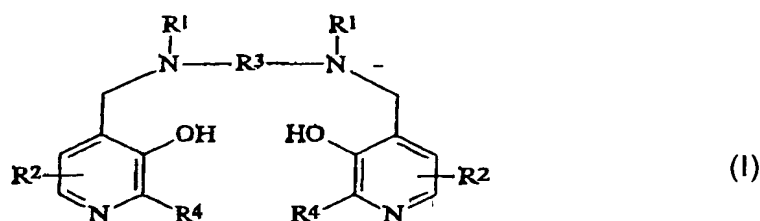
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56(new). A method as claimed in claim 51 wherein said manganese complex or salt thereof is administered at a dosage of 0.005 to 0.2 mmol/kg bodyweight.

57(new). A method as claimed in claim 56 wherein said manganese complex or salt thereof is administered at a dosage of 0.01 to 0.05 mmol/kg bodyweight.

58(new). A method as claimed in claim 51 wherein said manganese complex is a manganese chelate complex having a K_a value of from 10^7 to 10^{25} .

59(new). A method as claimed in claim 58 wherein said manganese chelate comprises a chelating compound of formula I:



or a salt thereof

(wherein in formula I

each R^1 independently represents hydrogen or $-\text{CH}_2\text{COR}^5$;

R^5 represents hydroxy, optionally hydroxylated alkoxy, amino or alkylamido;

each R^2 independently represents a group XYR^6 ;

X represents a bond, or a C_{1-3} alkylene or oxoalkylene group optionally substituted by a group R^7 ;

Y represents a bond, an oxygen atom or a group NR^6 ;

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R^6 is a hydrogen atom, a group $COOR^8$, an alkyl, alkenyl, cycloalkyl, aryl or aralkyl group optionally substituted by one or more groups selected from $COOR^8$, $CONR^8_2$, NR^8_2 , OR^8 , $=NR^8$, $=O$, $OP(O)(OR^8)R^7$ and OSO_3M ;

R^7 is hydroxy, an optionally hydroxylated, optionally alkoxyated alkyl or aminoalkyl group;

R^8 is a hydrogen atom or an optionally hydroxylated, optionally alkoxyated alkyl group;

M is a hydrogen atom or one equivalent of a physiologically tolerable cation;

R^3 represents a C_{1-8} alkylene group, a 1,2-cycloalkylene group, or a 1,2-arylene group; and

each R^4 independently represents hydrogen or C_{1-3} alkyl).

60(new). A method as claimed in claim 59 wherein in formula I:

R^5 is hydroxy, C_{1-8} alkoxy, ethylene glycol, glycerol, amino or C_{1-8} alkylamido;

X is a bond or a group selected from CH_2 , $(CH_2)_2$, CO, CH_2CO , CH_2CH_2CO or CH_2COCH_2 ;

Y is a bond;

R^6 is a mono- or poly(hydroxy or alkoxyated) alkyl group or a group of the formula $OP(O)(OR^8)R^7$; and

R^7 is hydroxy or an unsubstituted alkyl or aminoalkyl group.

61(new). A method as claimed in claim 59 wherein in formula I, R^3 is ethylene and each group R^1 represents $-CH_2COR^5$ in which R^5 is hydroxy.

62(new). A method as claimed in claim 59 in which the compound of formula I is N,N'-bis-(pyridoxal-5-phosphate)-ethylenediamine-N,N'-diacetic acid (DPDP) or N,N'-dipyridoxyl-ethylenediamine-N,N'-diacetic acid (PLED).

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63(new). A method as claimed in claim 58 wherein said chelate complex is a complex of a linear, branched or macrocyclic chelant selected from polyaminopolycarboxylic acid chelants and carboxylic acid derivatives thereof.

C1
cont.
64(new). A method of detecting myocardial ischemia in a human or non-human body, said method comprising administering to said body a contrast medium comprising a physiologically acceptable manganese chelate complex, subjecting said body to a magnetic resonance imaging procedure capable of generating images with time intervals of less than 0.5 seconds and thereafter providing a series of images of the myocardium of said body whereby to identify regions of abnormal blood flow, wherein said complex has a K_a value of from 10^7 to 10^{25} and is a complex of a chelant selected from the group consisting of N,N,N',N'',N''-diethylenetriaminepentaacetic acid (DTPA) and 6-carboxymethyl-3,9-bis(methylcarbamoyl-methyl)-3,6,9-triazaundecanedioic acid (DTPA-BMA).

65(new). A method of evaluating the severity of myocardial ischemia in a human or non-human body, said method comprising administering to said body a physiologically acceptable manganese complex or salt thereof at a dosage of 0.001 to 0.2 mmol/kg bodyweight, subjecting said body to a magnetic resonance imaging procedure capable of generating images with time intervals of less than 0.5 seconds and thereafter providing a series of images of the myocardium of said body to indicate the degree of blood perfusion deficit in the myocardium.

66(new). A method of monitoring reperfusion of the myocardium of a human or non-human body, said method comprising administering to said body a physiologically acceptable manganese complex or salt thereof at a dosage of 0.001 to 0.2 mmol/kg bodyweight, subjecting said body to a magnetic resonance imaging procedure capable of generating images with time intervals of less than 0.5 seconds and thereafter

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providing a series of images of the myocardium of said body and identifying regions of reperfusion.

67(new). A method of discriminating between reversibly and irreversibly injured myocardial tissue, said method comprising administering to said body a physiologically acceptable manganese complex or salt thereof at a dosage of 0.001 to 0.2 mmol/kg bodyweight, subjecting said body to a magnetic resonance imaging procedure capable of generating images with time intervals of less than 0.5 seconds and thereafter providing a series of images of the myocardium of said body and discriminating reversibly from irreversibly injured tissue.

68(new). A method of distinguishing viable myocardial tissue from necrotic (infarcted) tissue, said method comprising administering to said body a physiologically acceptable manganese complex or salt thereof at a dosage of 0.001 to 0.2 mmol/kg bodyweight, within a period of from 3 to 6 hours following administration of said complex or salt thereof subjecting said body to a magnetic resonance imaging procedure capable of generating images with time intervals of less than 0.5 seconds and thereafter providing a series of images of the myocardium of said body and distinguishing viable myocardial tissue from infarcted tissue.

69(new). A method as claimed in claim 51 wherein said magnetic resonance imaging procedure is carried out within a period of up to 6 hours after the administration of said complex or salt thereof to said body.

70(new). A method as claimed in claim 51 wherein the contrast medium further comprises calcium chelate complexes.

71(new). A method as claimed in claim 51 wherein the contrast medium further comprises calcium or sodium salts.

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72(new). A method as claimed in claim 71 wherein the calcium salt comprises calcium chloride, calcium ascorbate, calcium gluconate or calcium lactate.

C¹ conc'd.
73(new). A method as claimed in claim 51 wherein the contrast medium further comprises physiologically compatible buffers.

74(new). A method as claimed in claim 51 wherein the contrast medium further comprises an antioxidant such as ascorbic acid or a reducing sugar.
